

THE DISPERSIBLE ALENDRONATE MICROPARTICLE FORMULATION

TECHNICAL FIELD

This invention relates to the pharmaceutical dosage forms that are packaged into
5 sachets, which contain therapeutic amounts of alendronate (alendronate sodium
or alendronate monosodium trihydrate) micro-particles that are prevented to be
released into saliva, and alginic acid or sodium alginate and at least one
sweetener or a mixture of sweeteners, to be administered orally after dispersed in
a glass of 250 ml. water.

10 The above mentioned invention is associated with the decrease of potential side
effects of alendronate that may arise in esophagus and stomach. The methods in
this invention are:

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- the use of sodium alginate or alginic acid to prevent oesophageal reflux,
ulcer and heartburn that may arise during alendronate use
 - prevention any irritation related to alendronate sodium during its passage
through esophagus by ensuring the release of it in stomach.

BACKGROUND OF THE INVENTION

20 Alendronate sodium is chemically described as (4-amino-1-hydroxybutylidene)
bisphosphonic acid monosodium salt trihydrate. Patients complain about
heartburn after use of alendronate. Alendronate sodium tablets are recommended
to be used with a glass of water. In U.S. Patent No. 5.853.759, it has been
25 disclosed that alendronate tablets taken without a glass of water may cause
irritation.

30 Currently therapies with alendronate may be grouped as permanent treatments
with daily doses and treatments to be applied with given intervals (once in three
days, once in a week or once in 15 days). It is known that in both treatment forms
alendronate causes disorders such as esophageal reflux, heartburn and
esophagitis. The patent with PCT application No. of WO 99/04773, relates to

alendronate treatment with given intervals such as its use once a week, once in two weeks or once a month to decrease its gastrointestinal side effects. Additionally, the use of the pharmaceutical compound in combination with H₂ receptor blockers and/or proton pump inhibitors is disclosed in this patent.

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The effervescent alendronate formulations are disclosed in U.S. Patent No. of 5.853.759 and in addition to that, procedures for preparing the liquid alendronate formulations are disclosed in PCT Application No. of WO 98/14196. In these patents, alendronate is in dissolved form, i.e., alendronate that gets in contact with saliva is the dissolved alendronate.

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In the patent with PCT Application No. of WO 01/01991, bisphosphonate tablets with improved surface characteristics have been disclosed.

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The patent with PCT Application No. of WO 02/00204 relates to gastric passage of alendronic acid and its salts, and the effect of tannic acid and super dispersants.

The patent with PCT Application No. of WO 98/56360 relates to rapid passage of bisphosphonate tablets through esophagus.

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In the patent with PCT Application No. of WO 97/39755, coated dosage forms that contain ibandronate in inner phase to ensure rapid release have been disclosed.

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The patent with PCT Application No. of WO 95/00881 contains studies associated with enteric coated alendronate pharmaceutical dosage forms. One of the different aspects of this patent from that study is the use of polymers as coating material that are resistant to gastric acid and are opened at intestinal pH.

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Sodium alginate is used in cases of gastrointestinal reflux, heartburn and esophagitis. In the Patent numbered EP-A-0059221, the protective effect of alginic acid and its water soluble salts in gastrointestinal channel have been disclosed. In the patent with PCT Application No. of WO 01/66119, the

compositions which cover the sachet formulations of alginic acid and sodium alginate are disclosed and these do not cover the combination of alendronate microparticles with sodium alginate and alginic acid that are coated with polymers resistant to salivary pH. It has been cited that sodium alginate disclosed in the patent with No. of 99/04773, may be used as an ingredient in preparation of pharmaceutical dosage forms but the addition of sodium alginate in therapeutic amounts to the formulation to compensate the esophageal reflux and gastric side effects of alendronate has not been cited. Sodium alginate or alginic acid may be obtained commercially from FMC or Monsanto (for example; Protanal LFR 5/60 or Munucol LB).

SUMMARY OF THE INVENTION

This invention relates to the pharmaceutical dosage forms that are packaged into sachets, which contain alendronate microparticles coated with a polymer resistant to salivary pH, and the therapeutic amount of alginic acid or sodium alginate and at least one sweetener or a mixture of sweeteners, to be administered orally after dispersed in a glass of 250 ml. water.

Side effects occur with alendronate depending on its irritation of esophagus. To prevent this irritation one of the approaches of this invention is to prevent the contact of alendronate particles with esophagus. To ensure this, alendronate particles are coated with a polymer resistant to salivary pH. Microparticles of alendronate may be prepared by extrusion-rolling, vessel or liquidized bed procedures. The prepared particles are coated with a polymer resistant to salivary pH in a vessel or liquidized bed. For the coating purposes polymers such as aminoalkylmethacrylate copolymers and polyvinyl acetate diethylaminoacetate polymers that are insoluble (neutral pH) in saliva, but soluble in gastric pH may be used. Eudragit E which that is commercially produced in Röhm Pharma can be used in the coating.

The prepared alendronate microparticles are mixed with sodium alginate in a dry environment. After adding the sweetener and the other excipients, the sachet is prepared

- 5 To provide a good taste to the formulation, aspartame, potassium acesulfame, sodium saccharine, sucrose and its derivatives, polyols such as mannitol and sorbitol and monoammonium glycyrrhizinate may be used alone or as a mixture.

- 10 In the manufacture of the sachets, diluents (i.e., lactose, microcrystalline cellulose) lubricants (i.e., magnesium stearate, talc and PEG 6000), disintegrants (i.e. carboxymethylcellulose, crospovidone, carboxymethyl starch), surfactants, flavors and aromas may be used alone or as mixtures.

- 15 To prevent irritant effect of alendronate in mouth and esophagus, alendronate particles are coated with polymers insoluble in neutral pH (neutral pH corresponds to salivary pH). This polymer should be soluble in the gastric pH (pH 1-4) but not in the salivary pH (pH 6-7.5).

- 20 The prepared dispersible microparticles sachet formulation when dispersed in a glass of 250ml. water at the degree of 25⁰C, alendronate should not be released from the coated alendronate particles preferably in 3 minutes. At the end of 3rd minute, the release of not more 10% w/v of alendronate is permissible.

- 25 When with the prepared dispersible microparticles sachet formulation, the dissolution assay is performed in 0.1 N HCl (gastric medium, pH 1.2) at 900 rpm (USP XXIV, paddle method) not less than 85% of alendronate should be dissolved at the end of the 30 minutes.

EXAMPLE

- a. The manufacture of the alendronate microparticles that are resistant to salivary pH

5 Alendronate particle are aggregated with the following mixture:

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| Alendronate | 13.05 mg - 91.35 mg |
| PVP K30 | 1 mg - 14 mg |
| Ethanol | 6 mg - 84 mg |

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By the use of the spray coating procedure, alendronate is aggregated with polyvinylpyrrolidone dissolved in ethanol. The aggregated particles are coated with the following mixture.

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| 15 | Eudragit E100 | 10 mg - 280 mg |
| | Ethanol | 50 mg - 400 mg |
| | Acetone | 50 mg - 400 mg |
| | Colloidal silica | 2 mg - 15 mg |

20 b. Preparation of the sachet

An amount equivalent to 10 mg alendronate acid is taken from the prepared coated microparticles.

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| 25 | Coated microparticles equivalent to 10 mg alendronic acid | 26 mg |
| | Sucrose | 4648.9 mg |
| | Sodium alginate (Protanal LFR 5/60) | 300 mg |
| | Saccharine sodium | 0.1 mg |
| | PEG 6000 (lubricant) | 25 mg |

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Dissolution Test

The dissolution test has been carried out in 900 ml of 0.1 N HCl (pH 1.2). It has been performed by the use of paddle method under the conditions given in USP XXIV at 50 rpm. At the end of 30 minutes, 89% of alendronate has been dissolved.

Dissolution test of alendronate from the mixture contained in the sachet in salivary pH (neutral pH, pH 6.5):

Since the prepared sachet mixture is to be used after it is dispersed in a glass of water; the mixture is dispersed in a glass of 250 ml. water at the degree of 25°C and 3 minutes after at pH 6.5 4% of alendronate has been dissolved.